[$aa^{79}$ is R or G;]

$aa^{80}$ is I or N;

$aa^{81}$ is A or L [a hydrophobic or small amino acid];

$aa^{82}$ is R or L;

$aa^{83}$ is G or R;

[$aa^{84}$ is a hydrophobic or small amino acid;] and

wherein:

either or both of the sequences: SEQ ID NO.: 38 or SEQ ID NO.: 41 [in the brackets] may optionally be absent or truncated at any bond within either sequence [within the brackets].

## REMARKS

Claims 1-26 are pending. Claims 22-26 remain pending, but are withdrawn from consideration as a non-elected invention under a restriction requirement.

There is basis in the claims as originally filed as well as throughout the specification for this amendment. For example, the specification at page 6, lines 3-6 disclose that the peptides of the present invention inhibit cytotoxicity. Claim 1 has been amended to further clarify the organization of the formula of the claimed peptides. The specification provides support, for example, see page 3, line 12 to page 4, line 5.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider the rejections of the claims, that he withdraw same, and that he pass the application to issue.

Applicants' undersigned representative appreciates the courtesy extended by Examiners Chan and Debrino for the interview that was held on November 6th. This was a useful and productive discussion in identifying potentially allowable subject matter.

Rejection of the claims under 35 U.S.C. §112, first paragraph.

Claims 1-21 are rejected under 35 U.S.C. § 112, first paragraph because the specification, while enabling for those particular peptides such as the sequences demonstrated to inhibit

cytolysis on pages 21 *et seq.* of the specification, allegedly does not reasonably provide enablement for all of the peptides encompassed by the claim language. Applicants respectfully assert that the claim amendments presented above obviate these rejections.

Applicants acknowledge with appreciation the Examiner's withdrawal of one of four remaining grounds of rejection of the claims under 35 U.S.C. §112, first paragraph. The Examiner has, however, maintained rejection of the claims on three grounds. In order to avoid repetition and because each of these grounds has been described by the examiner as involving the same underlying issue, namely, "which structures would reasonably be expected to have the recited functional activity," these grounds will be addressed together.

The Examiner has maintained the rejection of the claims because the specification allegedly fails to provide an enabling disclosure commensurate in scope with the claims. The Examiner has cited Applicants' teaching that certain peptides inhibit CTL activity and certain ones do not. Specifically, for example, the Examiner finds that the ordinary skilled artisan would consider the diversity of peptides as claimed unpredictable and cites the differential activity between HLA-B2702 and HLA-B2705, where the former blocks CTL response, while the latter fails to do so.

Applicants respectfully point out that neither HLA-B2705 nor dimers containing the amino acid sequence of HLA-B2705 are encompassed in claim 1 (either in its original form or as now twice amended). The amino acid sequence of HLA-B2705 includes threonine at position 80 (see specification at page 21, line 7). Yet, claim 1 only reads upon those dimers containing either isoleucine or asparagine at that position. As was emphasized in Applicants' response dated June 1, 1999, the specification expressly teaches that substitution of threonine for the residue at position 80 eliminates the ability of HLA-B2702 dimers to inhibit lysis and T cell proliferation (see specification at page 22, lines 17-18 and page 24, lines 17-19). Thus, contrary to the

Examiner's finding, claim 1 does not in fact "read broadly on peptides comprising residues 75-84 of any HLA-B alpha chain." (emphasis added).

In any event, Applicants now twice-amend claim 1 to further narrow the scope of peptides upon which it reads. This amendment more particularly points out that the range of amino acid residues claimed for positions 76, 79, 81, and 84 have been reduced. Although claim 1 continues to read upon the dimers disclosed in Table 1 of page 21 of the specification, including those derived from both HLA-B2702 and HLA-B7, it now more specifically points out which peptide variants are provided. For example, the 576 different possible analogs asserted by the examiner as encompassed within the claimed invention for homodimers containing residues 79-84 is reduced by the present amendment to a total of 16 possible analogs. (see February 1, 1999 Office action at page 3). If one considers residues 75-84, there are a total of 48 possible different analogs.

Finally, although Table 1 at page 21 of the specification includes only a subset of those peptides encompassed by claim 1, the specification elsewhere provides that many other variations of the dimers provided in Table 1 were tested and found to inhibit the proliferation of T cells. The examiner is specifically directed to page 24, lines 21-25 of the specification which teaches the use of a serene scan. Use of this scan on the dimers B2702.84-75/75-84 and B2702.84-79/79-84 demonstrated that the replacement of any of the residues of these dimers other than at positions 78, 80 or 82 did not have a diminishing effect on the inhibition of T cell proliferation. Thus, this disclosure provides clear guidance on a structural basis as to the types of modifications that can be made to peptides without altering the claimed inhibitory effect.

In sum, Applicants respectfully assert that the specification provides clear guidance to the skilled artisan, not ambiguous or contradictory teachings, that the claimed dimers inhibit proliferation of lymphocytes. In view of the assays presented, such as measuring a decrease in the incorporation of $^{3}$H-thymidine and the use of a serine scan as taught in Example 1, the skilled

artisan would not be required to conduct undue experimentation to make and/or use the claimed invention. As explained in Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1213 (Fed. Cir. 1991), "it is not necessary that a patent applicant test all the embodiments of his invention, . . .; what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. . . . It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112." Thus, Amgen held that it was not necessary that a patent applicant disclose how to make and use every embodiment of a claimed invention. Rather, one must simply disclose "how to make and use enough sequences to justify grant of the claims sought." Id.

Applicants respectfully submit that the specification and amended claims meet this standard. The specification, with its disclosed testing of numerous embodiments and methods for the quick and systematic testing of others, reasonably provides enablement for the peptides encompassed by the amended claims. Accordingly, the Examiner's rejections may be properly withdrawn and claims as amended found allowable.

Rejection of the claims under 35 U.S.C. §103(a).

Claims 1-21 are rejected under 35 U.S.C. § 103(a) as obvious over Olsson (US PN 5,073,540) or WO88/05784. Each of Olsson and WO88/05784 teach peptide sequences relating to alleles of the MHC Class 1 antigens. Specifically, the examiner has found that although homo- or hetero-dimers containing a beta sequence are patentable over Olsson and WO88/05784, alpha-alpha dimers are unpatentable as obvious. This finding is based upon the examiner's conclusion that "one with ordinary skill in the art would at least expect that dimers of the same unit would exert the same functional effects as a monomer." (see August 16, 1999, Office action at page 3).

Applicants respectfully traverse this rejection. The specification clearly demonstrates that in fact, contrary to the examiner's conclusions regarding the expectations of those with ordinary skill in the art, dimers of the same unit exert a functional effect that is surprisingly disproportionate to that of its constituent monomers. For example, on page 22, lines 1-9 of the specification it is disclosed that although the alpha monomer HLA-B2702.75-84 was found to inhibit lysis, the alpha-alpha dimer B2702.75-84/75-84 did so at 5 times the potency. Contrasting this concrete evidence of an unexpected disproportionate result with the unsupported conclusions of the examiner, Applicants respectfully submit that the examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a). See, e.g., In re Wiechert, 370 F.2d 927, 152 USPQ 247 (CCPA 1967) (a 7-fold improvement of activity over the prior art held sufficient to rebut *prima facie* obviousness based on close structural similarity).

In light of the foregoing, Applicants respectfully submit that the rejections based upon 35 U.S.C. § 103(a) may be properly withdrawn and the claims found allowable.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: December 16, 1999

Respectfully submitted,

By: _____

Thomas D. Mays, Ph.D., J.D.
Registration No. 34,524

Morrison & Foerster LLP
2000 Pennsylvania Avenue, N.W.
Washington, D.C. 20006-1888
Telephone: (202) 887-8761
Facsimile: (202) 887-0763